Comments and suggestions from reviewer

Title: **WHO Global Model Regulatory Framework for medical devices including IVDs** (replacing the 2017 version published as Annex 4 in the WHO Technical Report Series 1003)

(WHO/GMRF/DRAFT/2 May 2022)

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(Table is expandable)

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General comments				
	As noted in the white paper, the International Medical Device Regulators Forum (IMDRF), formerly Global Harmonization Task Force (GHTF), has developed several well established and harmonized regulatory guidance for medical devices and combination products. IMDRF has updated/revised a number of previous GHTF guidance documents and has developed new documents of related concepts. It is important to cite the most relevant IMDRF and GHTF documents because some versions may be outdated or no longer used. The IMDRF website lists GHTF documents that are still current and has archived outdated documents. Please check IMDRF references for accuracy/relevance. https://www.imdrf.org/documents			

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Introduction				
Definition, classification, essential principles, and conformity assessment of medical devices				
282-287	There may also be products on the market that are similar to medical devices in function and risk that do not fit within these definitions. For reasons of protecting public health they are regulated as if they were medical devices. Examples include: impregnated bed nets to protect against malaria-bearing mosquitoes; personal protective equipment to avoid cross-infection; lead aprons to protect against radiation; some medical gases; and implantable or other invasive products for a cosmetic rather than a medical purpose (see Section 6).	Health authorities need a robust regulatory framework to appropriately classify and regulate medical products. Health authorities should not arbitrarily apply regulatory oversight of products under a medical device framework due to similarities in function or risk alone. For example, the document mentions impregnated bed nets to protect against malaria-bearing mosquitoes as an example of a product that should be regulated as a medical device. However, WHO has issued guidance on mosquito nets and does not consider them medical devices (https://www.who.int/news/item/15-08-2007-who-releases-new-guidance-on-insecticide-treated-mosquito-nets#:~:text=The%20new%20WHO%20guidance%20on,cost%2Deffective%20intervention%20against	This section needs to be removed without adequate discussion of this topic in Section 6. This section might be misinterpreted to enforce arbitrary and inappropriate regulatory controls over products that should not be considered medical devices.	

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		%20malaria.) and other health authorities have clarified that such products should be regulated under an environmental regulatory agency framework (https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM533600.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery) Also, there is no discussion of cosmetic products that may meet the definition of a medical device in Section 6 as indicated in this paragraph. Appropriate and clear regulatory requirements should be considered for certain cosmetic/aesthetic products that fall under the scope of a medical device regulatory framework to prevent substandard and unsafe products from entering the market.		
Section 2.2	Medical device classification and classification rules		Section 2.2 should reference and incorporate definitions and concepts from IMDRF guidance N64 on "Principles of In Vitro Diagnostic (IVD) Medical Devices Classification." https://www.imdrf.org/documents/principles-vitro-diagnostic-ivd-medical-devices-classification	

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Section 2.3	Principles of safety and performance		Section 2.3 should reference and incorporate concepts from the IMDRF guidance N47 on "Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices." https://www.imdrf.org/documents/essential-principles-safety-and-performance-medical-devices-and-ivd-medical-devices	
Enabling conditions for effective regulation of medical devices including IVDs				
501-502		Reference (11) is incorrect	Reference (11) should be changed to IMDRF guidance N64 on "Principles of In Vitro Diagnostic (IVD) Medical Devices Classification." https://www.imdrf.org/documents/principles-vitro-diagnostic-ivd-medical-devices-classification	
4.3.2.1.1 QMS Audit			Recommend including discussion of the Medical Device Single Audit Program (MDSAP) as a harmonized QMS auditing model that relies upon recognized third-party Auditing Organizations and work-sharing and reliance across	

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			regulatory authorities. MDSAP also includes an Affiliate MDSAP membership to enable reliance and information sharing on MDSAP certificates. https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap	
Establishing a stepwise approach to regulating medical devices				
1886-1889	Testing of medical devices can be conducted by the national control laboratory which is usually located within the national regulatory authority, by the National Reference Laboratory(s) or other external testing laboratories within or outside the country.	As worded, this section implies that medical device testing should be conducted by each jurisdiction under a national control laboratory. Repetitive medical device performance testing by each jurisdiction's national testing labs creates additional barriers and costs to device development which can limit patient access. Performance testing of medical devices can also be conducted by the medical device manufacturer in accordance with appropriate international consensus standards and performance testing that demonstrates conformance to essential principles.	Revise sentence to the following: Testing of medical devices can be conducted by the national control laboratory, which is usually located within the national regulatory authority, by the National Reference Laboratory(s), other external testing laboratories within or outside the country, **or by the medical device manufacturer in accordance with appropriate international consensus standards and appropriate performance testing that demonstrates conformance to essential principles.**	
Regulatory pathways				
Section 5.4 Line 2157	The medicine, devices, and biological products included in	General comment on the use of "constituent part." Several	The medicine, devices, and biological products included in	

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	combination products are referred to as constituent parts of the combination product. Depending on the applicable regulations, the medicine component of a combination product may be a pharmaceutical, radiopharmaceutical, natural health product, biologic, cell, tissue, organ, gene therapy, or human blood and its components.	instances throughout the section continue to use 'component' instead of 'constituent part'. There also needs be emphasis in this document on the on collaboration and coordination between the medicinal product sponsor and the device constituent part manufacturer in terms of product specification development, compatibility, design verification and validation, risk management, change control, product supply, complaint handling, and potentially, post marketing safety reporting.	combination products are referred to as constituent parts of the combination product. Depending on the applicable regulations, the medicine ~~component~~ **constituent part** of a combination product may be a pharmaceutical, radiopharmaceutical, natural health product, biologic, cell, tissue, organ, gene therapy, or human blood and its components. *Another example, line 2195:* Creating such a single regulatory pathway for combination products helps streamline their effective review, while taking into account the particulars of each ~~component~~ **constituent part** and protecting the health and safety of the public. A single regulatory pathway also helps avoid overlapping administrative requirements.	
Line 2150	Flowchart on Line 2150		The Flowchart that is shown on Line 2150 (page 860 should be reformatted because the flowchart does not fit on the page and cannot be read properly.	
1985-1988 AND 2000-2003			The English requires review please.	

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Section 5.4 Regulatory pathway for borderline products, Lines 2120-2124	After appropriate review and consultation, a product may be deemed to be subject to regulation as a medical device even though it may not clearly fall within the statutory definition of "medical device" e.g. cosmetic contact lenses, based on their documented potential for adverse health effects in wearers.	To avoid arbitrarily applying medical device rules and regulations to certain borderline products that may or may not meet a regulatory authority's statutory definition of a medical device, the decision should be made based on transparent feedback with the regulatory authority based on the product's technology, medical claims, intended use/indications for use, and primary mode of action.	After appropriate review and consultation, a product may be deemed to be subject to regulation as a medical device even though it may not clearly fall within the statutory definition of "medical device" **based on interpretation of the NRA's rules and regulations for medical product classification, technology, primary mode of action, medical claims made by the manufacturer, intended use and indications for use of the product**, e.g. cosmetic contact lenses **or drug eluting contact lens, wound-healing gel, etc**. The NRA may consider how certain products are classified and regulated by other well-established regulatory authorities.	
Section 5.5 Regulatory pathway for combination products Line 2172 - 2175	Specialized regulatory requirements for combination products generally are designed to address the overlaps and distinctions between the statutory and regulatory requirements applicable to the drug, device, and biological product constituent parts that comprise them. (26) (27)	References 26 and 27 not appear relevant to the statement on specialized regulatory requirements for combination products. Proposed revision to language should include risk-based considerations	Check and revise references 26 and 27 for accuracy please. Specialized regulatory requirements for combination products generally are designed to address the **risk-based considerations raised by the combined use of the constituent parts,** which may include	

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			overlaps and distinctions between the statutory and regulatory requirements applicable to the drug, device, and biological product constituent parts that comprise them. ~~(26) (27)~~	
Line 2181	In the interest of consistency, transparency and predictability, the national regulatory authority should adopt and publish guidance on how to: 1) determining what qualifies as a combination product 2) determining an appropriate regulatory pathway; and 3) establishing suitable pre- and post-authorization requirements.	Propose including a fourth item to capture streamlined GMP expectations for combination products	In the interest of consistency, transparency and predictability, the national regulatory authority should adopt and publish guidance on how to: 1) determining what qualifies as a combination product 2) determining an appropriate regulatory pathway; and 3) establishing suitable pre- and post-authorization requirements. **4) Establish streamlined GMP expectations for combination products. For example, regulatory authorities such as US FDA have developed a streamlined GMP approach for combination products under 21 CFR Part 4. https://www.fda.gov/media/90425/download**	
Line 2192 - 2197	To be predictable and transparent in their decision, the regulatory authority is best advised to employ a single regulatory pathway and develop criteria for determining the appropriate	Suggest replacing "single" with "streamlined", which is meant to capture a coordinated review process between the jurisdiction with the primary mode of action and the other review division.	To be predictable and transparent in their decision, the regulatory authority is best advised to employ a ~~single~~ **streamlined** regulatory pathway and develop criteria for determining the	

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	regulatory regime for combination products. Creating such a single regulatory pathway for combination products helps streamline their effective review, while taking into account the particulars of each component and protecting the health and safety of the public. A single regulatory pathway also helps avoid overlapping administrative requirements.	Note: more than one application or regulatory pathway may be expected for combination products that are cross-labeled or are referenced products and therefore single doesn't completely capture these types of products	appropriate regulatory regime for combination products.	
2199	This pathway determines both the type of application and the type of marketing authorization for the combination product. The designation may be based on the principal mechanism of action by which the product achieves its intended therapeutic or diagnostic purpose.	Replace principal mechanism of action with "primary/principal mode of action' and add definition to glossary This pathway should consider both a clinical study or clinical trial application as well as a marketing authorization application.	This pathway determines both the type of application and the type of marketing authorization or clinical trial requirements for the combination product. The designation may be based on the ~~principal mechanism of action~~ **primary/principal mode of action** by which the product achieves its intended therapeutic or diagnostic purpose. **Glossary:** Primary (Principal) Mode of Action (PMOA): The single mode of action of a combination product that makes the greatest contribution to the combination product's overall intended use(s).	

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Section 5.5 Regulatory pathway for combination products Line 2207	In some situations, elements of both medicine and device regulations may be applicable. (28) (29)	This sentence creates confusion with the recommendations in Section 5.5 such as lines 2168-2170: "The regulatory requirements for combination products arise from the statutory and regulatory requirements applicable to medicine, devices, and biological products, which retain their discrete regulatory identities when they are constituent parts of a combination product." Also, reference 28 refers to guidance on AI and ML medical devices which does not address combination products.	Recommend deleting sentence.	

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Section 5.5 Regulatory pathways for combination products			We recommend WHO consider instances when a combination product constituent (drug, biologic, or device) is developed by a third-party manufacturer with certain trade secret or confidential information that cannot be submitted under a single regulatory submission. For these situations, the regulatory authority should consider using a letter of authorized cross-reference which grants the regulatory authority to reference material from a third-party in the review of a combination product submission. Two potential sources of the referenced material could be from an existing marketing application or a master file which contains confidential information submitted to the regulatory authority directly from the third-party manufacturer. For more information, refer to: Guidance, Early Development Considerations for Innovative Combination Products: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/early-development-considerations-innovative-	

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			combination-products#clinical	
Line 2222	Reliance and recognition of medicine-device combination product may be a challenge due to the diversity and complexity of drug-device combination products. Because regulatory controls for drugs and medical devices may be different in different jurisdictions, it will be challenging to seek alignment with more than one regulator. Furthermore, a lack of clarity within regulations in different jurisdictions may lead to overlapping or conflicting regulatory requirements for a product. As there is no	We strongly recommend removing this paragraph. The end of the section on combination products should contain recommendations to continue international harmonization on combination products to drive consistency across jurisdictions rather than call out the current challenges that are known to industry and regulators.	Given the challenges with convergence and harmonization of combination products, global medical device stakeholders from the healthcare industry, manufacturers, and regulatory authorities should continue to engage in ongoing convergence and harmonization efforts through ICH, IMDRF, WHO etc.	

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	international harmonization guidance on combination products, national regulatory authorities using reliance or recognition may consider which requirements in other benchmark jurisdictions would best serve their country's needs.			
Additional topics				
6.4 New Medical Device Technologies: Software as a Medical Device (SaMD) and Software in a medical device (SiMD)			Given the diversity and proliferation of various software functions and technologies that may meet a regulatory authority's definition of a medical device, this section should introduce the concept of enforcement discretion for certain software functions that the regulatory authority exercises if the product poses a low risk to patients/users. For example, the FDA has issued guidance for certain software functions it has chosen to exercise enforcement discretion because of the low risk to patients. (e.g. Policy for Device Software Functions and Mobile Medical Applications https://www.fda.gov/media/80958/download). Enforcement discretion based on risk is especially important for	

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			regulatory authorities to focus regulatory controls and oversight on higher risk products given limited resources/capacity.	
Implementation				
References				
Glossary				
Add borderline product definition			Borderline Products: In the combined use context, medical products that offer combined characteristics that are covered by at least two legislations (e.g., both medical device and medicinal product), whose lead legislation within a jurisdiction may be unclear	
Add definition for PMOA			Primary (Principal) Mode of Action (PMOA): The single mode of action of a combination product that makes the greatest contribution to the combination product's overall intended use(s).	
Add definition of platform technology		We suggest the section on combination products contain a discussion on development of	Platform Technology: (i) A medical device, or medical device system, that may be suitable for	

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		platform technologies that streamline the development and regulatory review processes. This also may be applicable other sections on medical devices.	use with various drugs, and whose pre-existing device data and/or information can be leveraged, in whole or in part, to support such use ; (ii) biological products or drugs that serve as a foundation that can be built on to create variations on a therapeutic theme; (iii) a medicinal product formulation that may be suitable as a platform for use with various medical devices to enhance their performance.	
Other comments				